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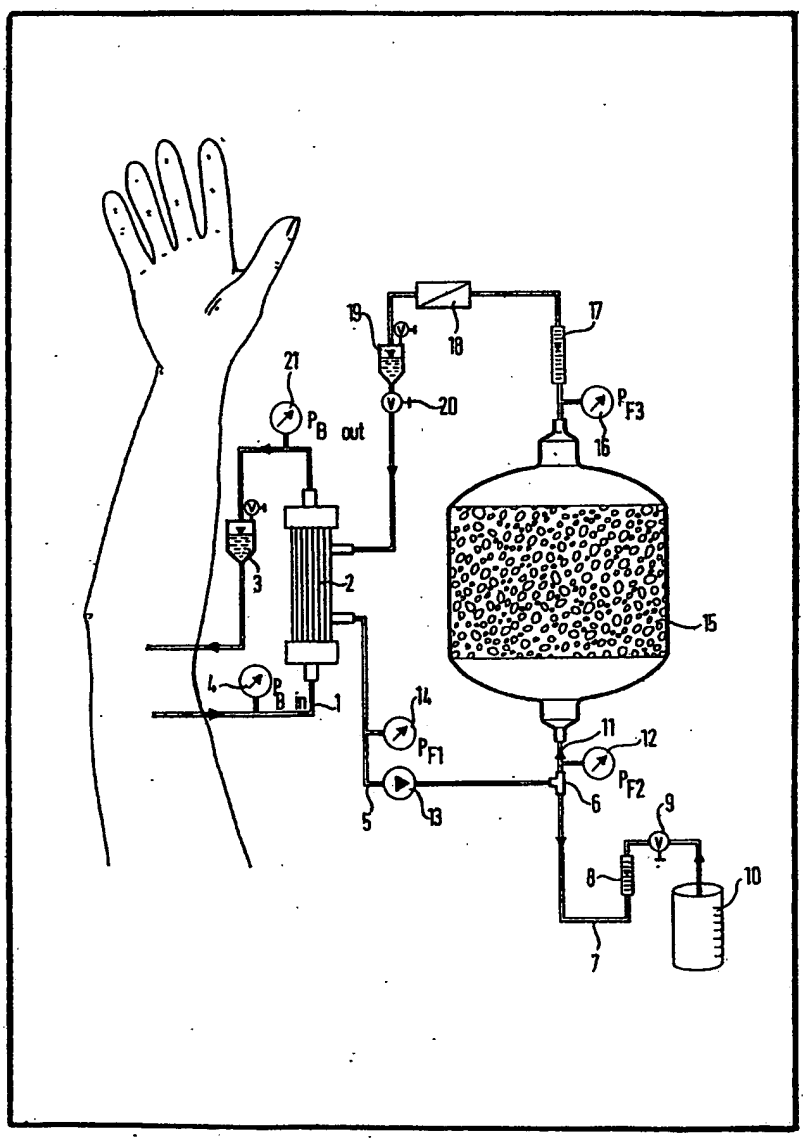
(54) Method and apparatus for the purification of blood

(57) A method and apparatus for the purification of blood based on a combined haemodialysis and haemofiltration. The liquid drawn off from the combined haemofilter and dialyser 2 is fed through an adsorption system 15 where it is regenerated, and is then returned to the haemofilter 2 in a circuit, so that the blood is "dialysed" there in the presence of its own regenerated filtrate, a portion of the drawn off liquid being removed by a branch 7 to remove haemofiltrate and maintain a constant fluid circulation. The liquid in the circuit may be dialysis liquid or ultrafiltrate.



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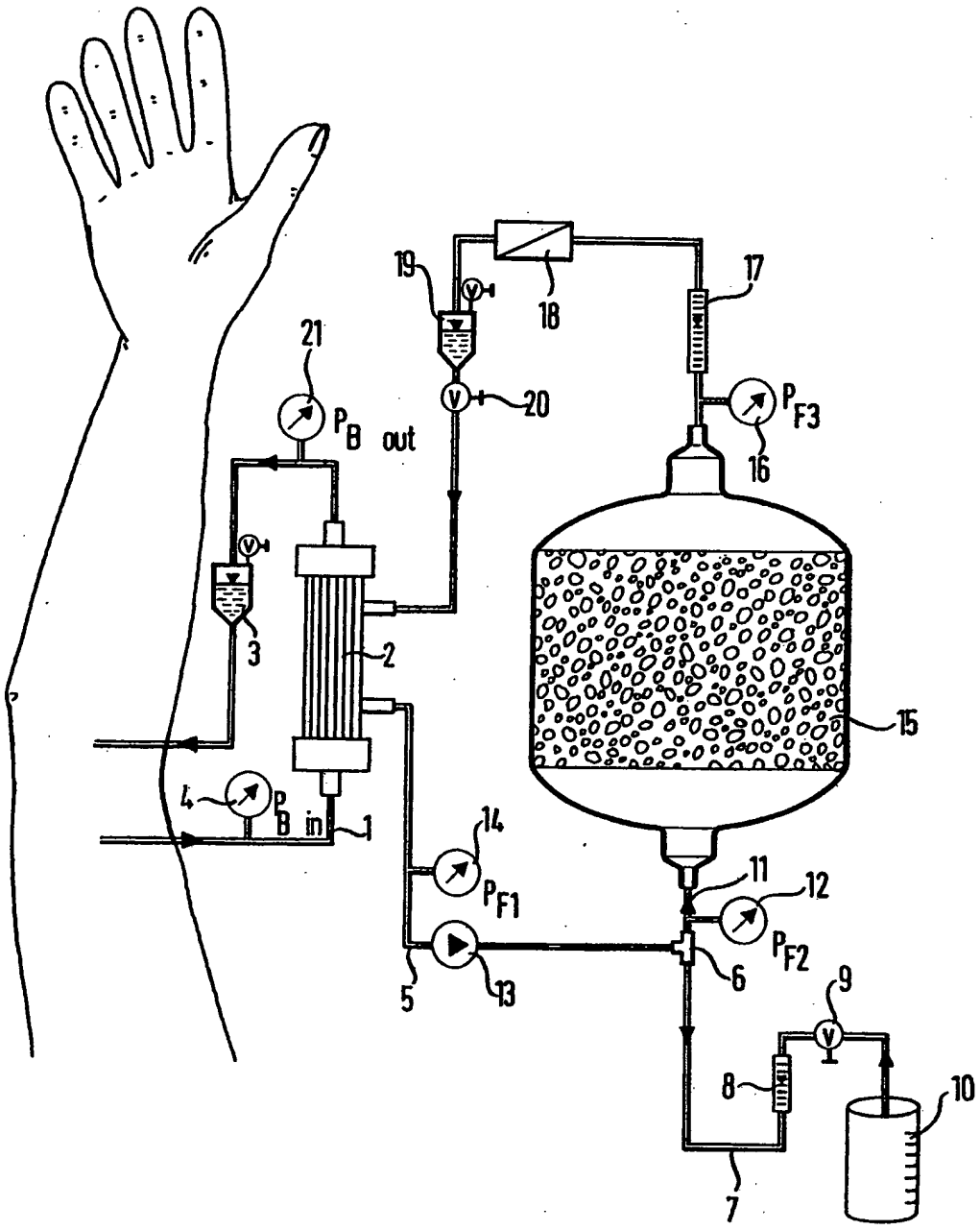
The drawing originally filed was informal and the print here reproduced is taken from a later filed formal copy.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SPECIFICATION

Method and apparatus for the purification of blood

This invention relates to a method for the purification of blood by the extracorporal elimination of, in particular, urinary substances by diffusion (haemodialysis) and the convective transport (haemofiltration) of these substances through a semi-permeable membrane, according to which arterial blood is conducted along one side (the blood side) of the membrane and dialysis fluid is conducted, under maintenance of a transmembrane pressure, along the other side (filtrate side) of the membrane in counterflow or in parallel flow to each other, and filtrate thus formed is removed from the membrane and disposed of.

It is known that the symptoms of a kidney inadequacy with acute or chronic kidney failure can be treated by means of extracorporal haemodialysis. With this dialysis method, the retention products or toxins are eliminaed by the diffusion process. They diffuse from the blood through a semi-permeable membrane into the dialysis fluid. The speed of diffusion is dependent on the relation between the size of the pores in the membrane and the molecular size of the substance to be eliminated, and also on the drop in concentration of the blood and dialysis fluid. The smaller the drop in concentration and the greater the molecular weight of a substance, the slower it is eliminated by the dialysis.

The method of haemodialysis has the disadvantage that in order to maintain a high drop in concentration, it is necessary to prepare large amounts of dialysis fluid. Therefore, in order to carry out the method, extensive installations are required which limit the mobility of the system with regard to its use as a portable artificial kidney. A further principal disadvantage of haemodialysis is that only substances with relatively small molecules (molecular weight<5000 Dalton) can be eliminated, since the elimination of substances from the blood occurs by means of a pure diffusion process.

In contrast to the dialysis method, metabolic products in natural kidneys are removed by filtration processes, that is, with the aid of a convective transport. During the years 1967—69, a method was developed which worked in sympathy with the operation of natural kidneys, in which the elimination of urinary substances was carried out exclusively by convective transport in the course of an ultrafiltration through a high grade permeable membrane. In this method known as "haemofiltration", ultrafiltrate is removed from the patient by use of a hydrostatic pressure, this being replaced by an infusion solution. One advantage of this method compared with the dialysis method is that, within a range limited by the diameter of the pores in the membrane and the flow of filtrate, all substances can be eliminated at the same speed, indpendent of molecular weight and size. Therefore, with this method, substances with a larger molecular weight (100000 Dalton and above), and in particular with high water contents, can be eliminated. This method has the disadvantage that, to compensate for the removal of fluid from the blood, a relatively expensive substitute solution must be fed into it, and that the method is not particularly effective with regard to the elimination of substances with a low molecular weight, since the elimination is carried out exclusively by convective transport.

In order to improve the removal of substances with a low molecular weight by a method of haemofiltration, combined methods have already been proposed which make use of both haemodialysis and haemofiltration (A. W. Leber, V. Wiezemann and F. Techart, Art. Organs, 4 (4), 1980, page 108). These methods correspond to the procedure first mentioned. By this means, dialysis fluid is conducted past the filtrate side of the semi-permeable membrane. Thus both a convective transport and a diffusion process take place on the membrane, so that, by this method, substances with small molecular weight and also with average to large molecular weight can be eliminated. The filtrate removed from the membrane is thereby completely disposed of. The method has the disadvantage that difficulities are encountered in controlling precisely the speed of filtration, and that here also large amounts of dialysis fluid and substitute solution are needed. By this means, the method has a limited "mobility" and therefore would appear scarcely suitable for use in the form of a portable artificial kidney.

The object of this invention is to produce a method for the purification of blood by which both substances with a small molecular weight and substances with an average to large molecular weight can be eliminated, without large amounts of dialysis fluid and substitute fluid being required. Moreover, the process may be embodied in an easily assembled and portable device, for example, a portable artificial kidney.

This object is achieved according to the invention by a method of the type first described, in that only part of the filtrate withdrawn from the membrane is disposed of, whilst the other part of the filtrate is conducted continuously through an adsorption system in which the filtrate is regenerated by the elimination of at least one part of the substances absorbed from the blood, and the regenerated filtrate is fed back in the circuit to the filtrate side of the membrane and is used there again as dialysis fluid.

In the method according to the invention, the blood is "dialysed", so to speak, in the ultrafilter (semipermeable membrane) against its own regenerated filtrate. Both the filtration speed and the circulation speed of the filtrate ar controlled by the negative pressure maintained on the filtrate side of the membrane. When the negative pressure on the filtrate side increases, the filtration speed also increases. It is preferable that, according to the invention, just sufficient filtrate is

disp sed of as to maintain an appr ximately constant circulation of fluid. In order t set the method according to the invention in motion initially, a relatively small amount of dialysis fluid is required (approximately 3—5 1.), which lies way below the amounts of dialysis fluid which have to be used in a customary haemodialysis. The negative pressure on the filtrate side of the membrane is produced by means of a filtrate pump. When the pressure on the filtrate side assumes a positive value, then this means that more fluid is being fed through the filter into the filtrate circuit than is being removed from the circuit. Then the speed of withdrawal must be increased in order to form a negative pressure on the filtrate side of the membrane once again and to maintain an approximately constant circulation of fluid. This can be achieved by opening a valve.

The principal advantages of the method according to the invention are that large amounts of dialysis fluid and substitute fluid are not needed, whereby only a relatively small proportion of the filtrate is disposed of which can be determined by the doctor in charge and is necessary for the dehydration of the patient. This means that, for carrying out the method according to the invention, low volume equipment only is needed for storing the dialysis fluid or the removed filtrate. Therefore the method can be carried out both simply and cheaply, whereby very high "mobility" is achieved.

With regard to the elimination of substances, both those with low molecular weight can be eliminated by a method comparable with the usual haemodialysis, and those substances with average or high molecular weight can be eliminated by a method comparable with haemofiltration. The method according to the invention thus combines the advantages of both the known processes, without necessitating large amounts of dialysis fluid and substitute fluid.

If the method according to the invention is to operate in the manner of an artificial kidney, then the adsorption system for regenerating the filtrate is set up in such a way that the predominant urea, creatine and uric acid is removed from the filtrate.

The method according to the invention is not, however, only limited to this area of use. Other substances, in particular toxic substances, can also be eliminated from the blood, so that the method can also be used, for example, on patients contaminated by drugs or poison, and generally in immunisation. The method can therefore have a substantially more widespread use than the known methods of haemodialysis and haemofiltration and their combinations, since the adsorption system can be adjusted to suit a particular need, that is, an adsorption system can be used of the type that will absorb the corresponding substances to be eliminated from th blood. As mentioned, when used as an artificial kidney, this will be a system absorbing predominant area, creatine and uric acid. In other cases, an adsorption system can b used which absorbs the corresponding substance to be eliminated.

Such a possibility of eliminating specific substances from the blood does not exist in the known methods. In haemodialysis and haemofiltration, the molecular size alone of the substances to be eliminated plays a part, that is, all substances under a certain molecular weight are removed from the blood, independent of whether they have toxic properties or not. On the other hand, according to the invention it is possible to remove one specific substance selectively by simply using an adsorption system adjusted to the specific substance.

In addition to the prior art, it should also be mentioned that it is already known that a haemoperfusion can be coupled with an ultrafiltration (T.M.S. Chang, E. Chirito, P. Barre, C. Cole, C. Lister and E. Resurreccion, Long-term Clinical Assessment Combined ACAC Hemoperfusion-Ultrafiltration in Uremia, Artificial Organs 3 (2), 1979, page 127). Hereby, blood is conducted directly over an active carbon column and is subsequently submitted to an ultrafiltration by means of a semi-permeable membrane, whereby the filtrate drawn off is completely disposed of. Although this method can be carried out relatively easily, there is the disadvantage that by this means the blood comes into direct contact with the active carbon filter, whereby blood cells can be destroyed. Thus a special type of active carbon must be used which is sealed in micro-capsules of cellulose nitrate. The method according to the invention does not present this disadvantage, since by this means only the filtrate separated off from the blood is fed through an adsorption system (active carbon filter), that is, in this case the adsorption system is not in direct contact with the blood.

For the foregoing reaons, in the method according to the invention it is also possible to operate with relatively high blood flows (greater than 150 ml/min), which is not possible in a method of haemoperfusion on account of possible damage to the blood particles and the danger of embolisms. Furthermore, in the method according to the invention the adsorption system does not need to be sterilised, since bacteria and viruses cannot get through the ultrafilter.

As already mentioned, the method according to the invention can also be used for the decontamination of blood with drugs and the removal of poison. In immunisation, it can be used for the removal of antigene-antibody aggregates and other proteins. For this purpose, instead of an ultrafilter a membrane filter with a pore size of 0.1 to 0.5 μm is used, and a corresponding adsorption material is used in the adsorption system.

The filtrate fed through the circuit is advantageously kept at body temperature. This is achieved, if necessary, by heating the filtrate fed through the circuit, preferably by conducting it through a heat exchanger.

The blood circulation on the blood side of the

membrane is carried out if possible without a blood pump, by making use of the body's own blood pressure. This pressure amounts to around 50—80 mm Hg, which is sufficient to drive 200—250 ml of blood per minute through a customary ultrafilter. In the method according to the invention, a filtration rate of between 10 to 50 ml/min is preferably used, which is very much lower than in a corresponding haemofiltration process. If the process is carried out on a patient to whom large amounts of fluid are conducted, then a higher filtration rate than 50 ml/min is used. Naturally, a blood pump can also be used.

When the method is to take on the function of an artificial kidney, it is appropriate for a membrane to be used whose cut-off lies between 5000 and 10000 Dalton. In using a membrane of this type, the above-mentioned filtration rate of 10 to 50 ml/min can be achieved with a relatively low transmembrane pressure. Preferably, a transmembrane pressure Δp_m of <200 mm Hg, in particular 80 mm Hg, is used. Since this value is comparatively very small, the danger of the membrane being ruptured and of the blood overflowing into the filtrate circuit is also slight.

In many applications, in particular when used as an artificial kidney, the method according to the invention is applied with active carbon in the adsorption system. By this means, a large proportion of the uraemic substances can be removed from the filtrate. Although the absorption ability of active carbon is relatively poor compared to urea, as yet no better material has been proposed for this purpose. It has been shown for example, that for the elimination of 40 g of urea, around 3 kg of active carbon and 3 litres extracted filtrate fluid are sufficient per treatment.

It is obvious that the filtrate cannot be recirculated before the filtrate circuit is completely filled with fluid. An alternative embodiment of the method according to the invention is commenced in such a way that the filtrate circuit is filled at the outset with fresh dialysis fluid. However, if it is not desired that it should be filled with dialysis fluid, then, according to another embodiment of the method, the treatment can be commenced with a quick, pure ultrafiltration, until the filtrate circuit is filled. Accordingly, the filtrate in the filtrate circuit serves as the dialysis fluid. By this means, no extraneous dialysate is necessary.

Accerding to the invention, an adsorption system can be used which is divided into three or more small systems, which are arranged either parallel to each other or in series one behind the other. With the latter variation, a saturated adsorption cartridge can easily be replaced by a fresh adsorption cartridge. This variation permits the method to be carried out by means of a device which can be carried about on the body. If, for example, several adsorption cartridges are placed parallel to each other, care should be taken that each cartridge has an identical drop in pressure, so that the same rate of flow prevails throughout.

The method according to the invention is therefore very flexible with regard to the formation of the adsorption system, since the number of cartridges used can be suited to the respective requirements. The cartridges used can be very quickly regenerated. Thus an active carbon column, for example, can be regenerated by steam and can be used again for the same patient, whereby the treatment is altogether cheaper than with other systems. This is of advantage in cases where no fresh cartridges are available. Also by means means storage of fresh cartridges can be avoided.

Furthermore, the invention relates to apparatus for carrying out the above-described method, with a first conducting system for the production and maintenance of an extracorporal blood flow from an artery to a vein, a haemofilter connected to the first conduction system with a semi-permeable membrane along one side of which the blood is conducted, and a second conduction system for conducting the dialysis fluid, whilst maintaining a transmembrane pressure, along the other side of the membrane in counterflow or in parallel flow to the bloodstream, so that haemodialysis and haemofiltration takes place, and for carrying off or disposing of the filtrate removed by the membrane.

This apparatus is characterised according to the invention in that the second conduction system has a branching point downstream from the haemofilter, from which point a tube for the production and maintenance of a filtrate circuit leads back to the haemofilter, whilst another tube serves to carry off the filtrate, that a filtrate pump and an adsorption system, downstream from the branching point, are arranged in the filtrate circuit between the haemofilter and branching point, and that a shutoff valve or metering valve, for controlling the amount of circulated fluid, is placed in the tube serving to carry away the filtrate.

The appartaus according to the invention is characterised by simple construction and easy handling, and also great mobility. This makes it particularly suitable for use as an artificial kidney which can be carried on the body. By this means, by controlling the shutoff valve or metering valve which is arranged in the tube serving to carry away the filtrate, the amount of circulated filtrate or the amount of filtrate being carried away can be easily controlled, particularly manually. There is the possibility of a range of variations for the adsorption system, which permit a speedy exchange and replacement of used adsorption elements which can be quickly regenerated.

An embodiment of the device is now described in detail with reference to the drawing. The drawing shows diagrammatically the construction of apparatus according to the invention in the form of an artificial kidney.

The apparatus comprises a first conduction system 1 for the production and maintenance of the extra-corporal bloodstream from an artery to a vein. In this conduction system there is a

haemofilter 2 which can b of a known construction, for exampl , an Amicon diafilter, an Asahi haemofilter or an RP-6 haemofilter. The cut-off of the semi-permeable membrane of the filter can, in the embodiment shown here of an artificial kidney, reach a molecular weight of up to 100000 Dalton. For other applications, still higher cut-offs are possible. Manometers 4, 21 are arranged upstream and downstream of the haemofilter 2. Furthermore, a blow valve 3 is provided in the conduction system 1. The system described here usually manages without the use of a blood pump in the conduction system 1, since the pressure drop in the above-mentioned haemofilters is small. Moreover, it can be operated with a relatively low transmembrane pressure Δp_m of below 200 mm Hg, preferably around 8 mm Hg. Thereby the system is further simplified, and no damage occurs to the blood filter.

Moreover, the apparatus has a second conduction system 5 which, in connection with a tube 11, serves to produce and maintain a filtrate circuit. By means of this filtrate circuit 5, 11, the filtrate which is drawn off from the blood throough the semi-permeable membrane by diffusion and convective transport, that is, by haemodialysis and haemofiltration, is circulated, whereby it is regenerated by being fed through an adsorption system 15. The blood is therefore "dialysed" in the haemofilter 2 against its own regenerated filtrate. A filtrate pump 13 is used to circulate the filtrate, this pump determining both the filtration speed and the circulation speed. The pump sucks the filtrate through the semi-permeable membrane and then pushes it through the adsorption system 15. In order to control the pressure drop in the filtrate circuit, a shutoff valve or metering valve 20 is provided between the adsorption system 15 and the haemofilter 2.

The filtrate pump 13 is naturally arranged downstream from the haemofilter 2 and is upstream from a branching point 6 in the conduction system at which the tube 11 for forming the filtrate circuit and a tube 7 for eliminating or carrying off the filtrate removed by the membrane branch off. A further shutoff valve or metering valve 9 is provided in the tube 7, by means of which valve the amount of filtrate which is circulated or carried off can be controlled, in particular manually. The amount of filtrate which is carried off can, for example, be conducted into a container 10 in which it is stored and disposed of at a later date. A flowmeter 8 is preferably arranged in the tube 7.

Moreover, the filtrate circuit 5, 11 contains a heat exchanger 18 in the embodiment shown here, which is used to keep the circulating filtrat at body temperature, a blow valve 19 for ventilation and a flowmeter 17. Furthermore, manometers 12, 14, 16 are arranged in the circuit.

The apparatus described above operates in such a way that firstly, the filtrate circuit 5, 11 is filled with a conventional dialysis fluid. The valve 9 is normally cl sed, whilst the valve 20 is opened. When th filtrate circuit has been filled with dialysis fluid, the filtrate pump 13 is put into operation, whereby the dialysis fluid or the filtrate is circulated. By means of the valves 9 and 20, the flow can be controlled in such a way that only sufficient filtrate to maintain a constant fluid circulation is carried off into the container 10. In other words, when the pressure in the filtrate circuit on the filtrate side of the membrane assumes a positive value, then this means that the fluid transport through the membrane into the filtrate circuit is greater than the fluid offtake into the container 10. By adjusting the valve 9, equilibrium can be obtained again easily, and vice versa. This can be carried out by the patient himself after suitable medical instruction.

In the embodiment described here, around 3 kg of active carbon in the adsorption system and 3 litres of extracted filtrate are necessary per treatment for the elimination of approximately 40 g of urea. The complete device therefore weighs no more than 8 kg, including the dialysis fluid, the filtrate pump, the valves etc. Therefore the device is considerably lighter than known systems and can be carried around on the body of the patient.

When used as an artificial kidney, as is the application described here, active carbon is preferably used for regenerating the filtrate. This can be in the form of cartridges, so that a quick exchange of used cartridges for new ones is possible. By this means also, several cartridges can be placed parallel to each other or in series one behind the other. Instead of active carbon Redy cartridges can also be used, but these have the disadvantage that they require a greater amount of dialysis fluid.

If it is not desirable for the filtrate circuit to be filled initially with dialysis fluid, the treatment can also be commenced with a quick, pure ultrafiltration, until the filtrate circuit is filled. Then the haemodialysis can be started against the regenerated filtrate.

The method of operation of the above-described device is confirmed by the following test:

An Amicon hollow fibre filter H1x50 (930 cm^2 surface) was used as a haemofilter, and 120 g of extruded active carbon, which had been thoroughly washed, was used for regenerating the filtrate. In this test, a urea and uric acid solution (1500 ml) was used as blood. This solution was circulated through the filter at a speed of 200 ml/min, so that a filtration speed of 10 ml/min resulted, which was maintained together with the circulation speed of 200 ml/min. At regular intervals, samples were taken of the "blood" present in a container and of the filtrate leaving the active carbon column, so as to determine the urea and uric acid content.

The tests gave the result that, after a 60 minute treatment time, the concentration of uric acid in the "blood container" had been reduced t nil. The amount of urea removed amounted to 1 g.

Claims

1. A method for th purification of blood by the extracorporal elimination of, in particular, urinary substances by diffusion (haemodialysis) and the convective transport (haemofiltration) of these substances through a semi-permeable membrane, according to which arterial blood is conducted along one side (the blood side) of the membrane and dialysis fluid is conducted, under maintenance of a transmembrane pressure, along the other side (filtrate side) of the membrane in counterflow or in parallel flow to each other, and filtrate thus formed is removed from the membrane and disposed of, wherein only one part of the filtrate removed from the membrane is disposed of, whilst the other part of the filtrate is continuously conducted through an adsorption system in which the filtrate is regenerated by removing at least part of the substances absorbed from the blood, and the regenerated filtrate is returned in a cycle to the filtrate side of the membrane and is used there again as dialysis fluid.

2. A method according to claim 1, wherein just sufficient filtrate is disposed of as to be able to maintain a constant fluid cycle.

3. A method according to claim 1 or claim 2, wherein the filtrate conducted in a cycle is kept around body temperature, if necessary by heating.

4. A method according to any one of the preceding claims, wherein the operation is carried out at a filtration rate of between 10 to 50 ml/min.

5. A method according to any one of claims 1 to 3, wherein a filtration rate higher than 50 ml/min is used when the method is carried out on a patient, to whom large amounts of fluid are conducted.

6. A method according to any one of the preceding claims, wherein a membrane is used, the cut-off of which lies at a molecular weight of between 5000 and 100000 Dalton.

7. A method according to any one of the preceding claims, wherein a transmembrane pressure Δp_m of less than 200 mm Hg is used.

8. A method according to claim 7, wherein a transmembrane pressure of 80 mm Hg is used.

9. A method according to any one of the preceding claims, wherein the blood circulation on the blood side of the membrane is carried out without a blood pump by making use of the body's own pressure gradient.

10. A method according to any one of the preceding claims, wherein the method is commenced by filling the filtrate circuit with fresh dialysis fluid.

11. A method according to any one of claims 1 to 9, wherein the method is commenced with a quick, pur ultrafiltration, until the filtrate circuit is filled, whereby the haemodialysis is started against the regenerated filtrate.

12. A method according to any on of the preceding claims, wherein an adsorption system is used which is divided into three or more small systems, which are arranged either parallel to each other or in series one behind the other.

13. Apparatus for carrying out the method according to any one of claims 1 to 12, comprising a first conducting system for producing and maintaining an extracoporal blood stream form an artery to a vein, a haemofilter with a semi-permeable membrane connected to the first conducting system, the blood being conducted along one side of this membrane, and a second conducting system for conducting dialysis fluid, under the maintenance of a transmembrane pressure, along the other side of the membrane in counterflow or in parallel flow to the bloodstream, so that a haemodialysis and a haemofiltration takes place, and for carrying off the filtrate drawn off by the membrane, wherein the second conducting system has a branching point downstream from the haemofilter, from which point a tube for producing and maintaining a filtrate cycle leads back to the haemofilter, whilst another tube serves to carry away the filtrate, wherein a filtrate pump and, downstream from the branching point, an adsorption system are arranged in the filtrate circuit between the haemofilter and the branching point.

14. Apparatus according to claim 13, wherein a shutoff valve or metering valve is provided in the filtrate circuit for the normal control of the pressure drop, this valve being connected to the adsorption system at the outlet end.

15. Apparatus according to claim 13 or claim 14, and in the form of an artificial kidney which can be fitted to the body.

16. Apparatus according to any one of claims 13 to 15, wherein the adsorption system comprises at least one active carbon column or cartridge.

17. Apparatus according to claim 16, wherein several activated carbon columns or cartridges are arranged parallel to each other or in series.

18. Apparatus according to claim 15, wherein the haemofilter has a cut-off for a molecular weight of between 5000 and 100000 Dalton.

19. Apparatus according to any one of claims 13 to 18, wherein a heat exchanger is arranged in the filtrate circuit.

20. Apparatus according to any one of claims 13 to 19, wherein the filtrate pump is a miniature pump.

21. Apparatus according to claim 20, wherein the miniature pump is a miniature roll pump or a minuature membrane pump.

22. Apparatus according t any on of th preceding claims, wherein the adsorpti n system is composed of various specifically acting adsorbents.

23. A method for the purification of blood substantially as her inbefore described with reference to the accompanying drawing.

24. Apparatus for the purificati n of blood substantially as hereinbefore described with reference to the accompanying drawing.

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